

II. Rejection Over Real et al.

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Claim 62 is rejected as anticipated by Real. The examiner maintains the position that the Real reference discloses an antigen that reads on the present claim 62. In order to more clearly identify and distinctly claim their invention, applicants have amended claim 62 to include the recitations of claims 67, 68 and 71. This also serves to distinguish the antigen of Real, as evidenced by the lack of any rejection of claims 67, 68 and 71 over Real. Reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejection Over Euhus et al., Rote et al., Finck et al., Pharmacia, Ljungquist and Goldenberg

The examiner now has alleged that, though Euhus does not anticipate the claims, its teachings, when combined with various secondary references, obviate all of the pending claims. Applicants respectfully traverse.

Euhus is cited as disclosing UTAA and methods for its isolation. Rote is said to teach detection of tumor-associated antigens detected by autologous sera in the urine of patients with solid neoplasms. The antigen is said to be heat stable at 100°C for 60 min., and has a molecular weight of 10⁶ daltons, which dissociates into smaller subunits by treatment with 6M urea. Finck is said to teach tumor-associated antigens in the urine of patients with colon carcinoma. The antigen is larger than 10⁶ daltons and is heat stable at 100°C. The Pharmacia reference is cited for gel filtration techniques. Ljungquist is said to teach purification of endonuclease IV by a combination of

ammonium sulfate, gel filtration, heat and DNA-cellulose chromatography. Goldenberg teaches the production of antibodies to CEA.

At the outset, the rejection is traversed on the same basis as argued in the previous responses - that the Euhus reference is not enabling. As discussed extensively on the record, the teachings are Euhus are not sufficient to permit one to reproducibly make and use the invention. The examiner's arguments to the contrary merely highlight that the reference, at best, provides an invitation to one of skill in the art to *try* to reproduce the invention while sifting through a variety of technologic parameters that may or may not result in obtaining of a purified antigen composition comprising UTAA. This is not the standard for obviousness, however, and the present evidence already shows why this rejection is improper. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). However, applicants will once again delve into the specifics of the rejection and provide *additional* evidence from another unchallenged source as to why the rejection is improper.

1. Parameters Necessary for the Isolation of UTAA from Urine

The examiner argues that the Pharmacia reference teaches how to isolate proteins using ion exchange and gel filtration. This is not contested. The examiner also provides an extensive discussion of how one could use autologous sera to find such antigens once they had been fractionated. However, this clearly is a circular argument and is an essential flaw in the examiner's reasoning. Assuming one could isolate *some* fraction containing UTAA, how would one know that they had purified the correct antigen *or* the correct antibodies, much less a patient that even contained these substances? The answer, of course, is that they could not know since the prior art

fails to teach which fraction contained UTAA, or how one could identify UTAA from any other
protein using any readily obtainable, well characterized antibodies.

need a ref. for ELISA / check note & trick - describe how to use complement fixation assay
Method works

Thus, what the examiner is proposing is that the skilled artisan go back to "square one" and repeat applicants' invention without any significant assistance from the cited art. Whether or not they would achieve the same result, *i.e.*, the claimed invention, is entirely up to chance -- chance that the skilled artisan would select the proper parameters for purification, chance that the skilled artisan would select the proper starting materials, and chance that the skilled artisan would pick the appropriate purified fraction (by either guessing, or by using an antibody source which itself would be selected on the basis of chance). In sum, the examiner's proposal is nothing but a recitation of serendipity that is devoid of the *likelihood of success* that is required for legal obviousness. *In re O'Farrell*.

Ab source for ELISA and complement fixation assay
w/ from patient i colon carcinoma as taught by Trick.

2. Structure and Immunological Profile of UTAA

The examiner next argues that proteins can be isolated without knowledge of their amino acid sequence. In addition, it is argued by the examiner that the present disclosure, with respect to UTAA structure, is the same as that presented in the Euhus reference. Finally, it is argued that antibodies to UTAA are "known," and hence, their disclosure "is not any different from that of the claimed monoclonal antibody against the claimed UTAA."

While it is true that there is no disclosure of an amino acid sequence, the present disclosure contains considerably more information with regard to how one goes about purifying UTAA

specifically, not how one goes about purifying proteins generally. Thus, the fact that there is no sequence is quite problematic - the prior art is nothing more than a general disclosure of techniques that *might* purify UTAA without any indication of how to confirm this or to identify which fraction actually contained UTAA. On the other hand, by following the teachings in the instant specification, one can, without any doubt, isolate highly pure UTAA.

As to the equivalence of the disclosed monoclonal antibody and patient serum, applicants again ask the examiner how one could determine that the serum the skilled artisan would choose to use would bind to UTAA, as opposed to some other antigen? Again, the answer is that one would *not* know. To the contrary, the skilled artisan could take the antibody disclosed in the present application, AD1-4OF4, is unique in its ability to identify UTAA. This antibody is disclosed in the present application and, if the examiner believes it would advance the prosecution, applicants would be willing to deposit the antibody with a Budapest Treaty authorized depository.

3. The Shively Declaration

In previous responses, applicants provided the examiner with two declarations from Dr. Ralph Reisfeld, Head of the Division of Tumor Biology at the Scripps Research Institute. In a first declaration, Dr. Reisfeld opined that one of skill in the art, upon reading the Euhus abstract, could not expect to reproduce the invention given the scant teachings provided therein. In particular, it was argued that the skilled artisan would not know the key conditions (ionic strength, pH, retention times) under which a successful isolation was to be performed. In another declaration, Dr. Reisfeld noted that the abstract also contained no information on the sequence or immunogenic identity of

the claimed antigen and, thus, even if it could be isolated, the skilled artisan would not know that the antigen was the same as that claimed. Thus, based on his extensive experience, Dr. Reisfeld found the Euhus disclosure as lacking a teaching sufficient to permit one of skill in the art to repeat the claimed invention.

Rather than accepting this expert affidavit, the examiner has improperly chosen to substitute her own opinion for that of the declarant. However, in an effort to advance the prosecution, applicants offer yet another declaration, this one from Dr. John Shively, Chairman of Immunology at the Beckman Research Institute, City of Hope. Therein, Dr. Shively explains that the Euhus abstract "does not contain sufficient information to enable purification of UTAA." This opinion was based on the facts that (i) the abstract describes the purification of antigen antibody complexes that contained numerous other species, and (ii) there was insufficient information on how to purify UTAA from this heterogeneous composition. Further, Dr. Shively notes that only in later, post-published papers, were the specific parameters necessary for purification of UTAA finally spelled out.

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Thus, it again is submitted that there is overwhelming declaratory evidence that rebuts the examiner's position regarding the teachings of the Euhus abstract. The reference is nothing more than an invitation to the skilled artisan to try to isolate and uncharacterized antigen. Without more, this abstract cannot be considered to provide the essential "enabling methodologies" or the "reasonable likelihood of success" that are required for a *prima facie* case of obviousness. *In re O'Farrell.*

4. *Individual Teachings of the Secondary References*

Moving on the teachings of the individual references, one can easily dismiss the significance of Ljunquist, Goldenberg and the Pharmacia disclosure. Again, it is not contested that proteins can be isolated, nor is it argued that antibodies cannot be produced against many purified antigens. Similarly, applicants do not argue that ion exchange chromatography or gel filtration themselves are inoperable. These teachings do not provide any indication as to how these procedures should be applied to the present invention, however, and as such, contribute little to the body of knowledge that would, according to the examiner, place the claimed invention within the grasp of the public. They merely constitute generally related background methodologies that are as relevant to the present invention as they are two thousands of similar, but unrelated inventions.

The only disclosures that bear upon UTAA are the sketchy teachings of Rote and Finck which, as far as the action is concerned, only establish that the described antigens are heat stable to 100°C, a fact that can hardly be said to remedy the problems outlined above with respect to reproducibility. Again, it must be emphasized that the claims are drawn to a unique tumor antigen composition, not to methods by which such an antigen hypothetically could be produced. As the examiner is well aware, there is a legal requirement, for *any* prior art rejection, that the references be enabling. Here, there are no enabling disclosures for UTAA.

In light of the declarations of record, and the considerable discussion of why the rejections are inapplicable, applicants respectfully submit that the record contains overwhelming evidence that

such is not the case for the Euhus reference, or any other art being advanced. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

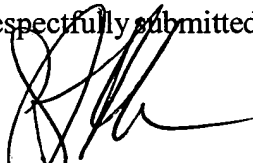
IV. Conclusion

In light of the foregoing comments and remarks, applicants respectfully submit that all claims are in condition for allowance, and a early notification to that effect is solicited. Should the examiner have any questions regarding this response, applicants invite the examiner to call their undersigned representative at the telephone number listed below.

May 4, 1998

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Respectfully submitted,



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